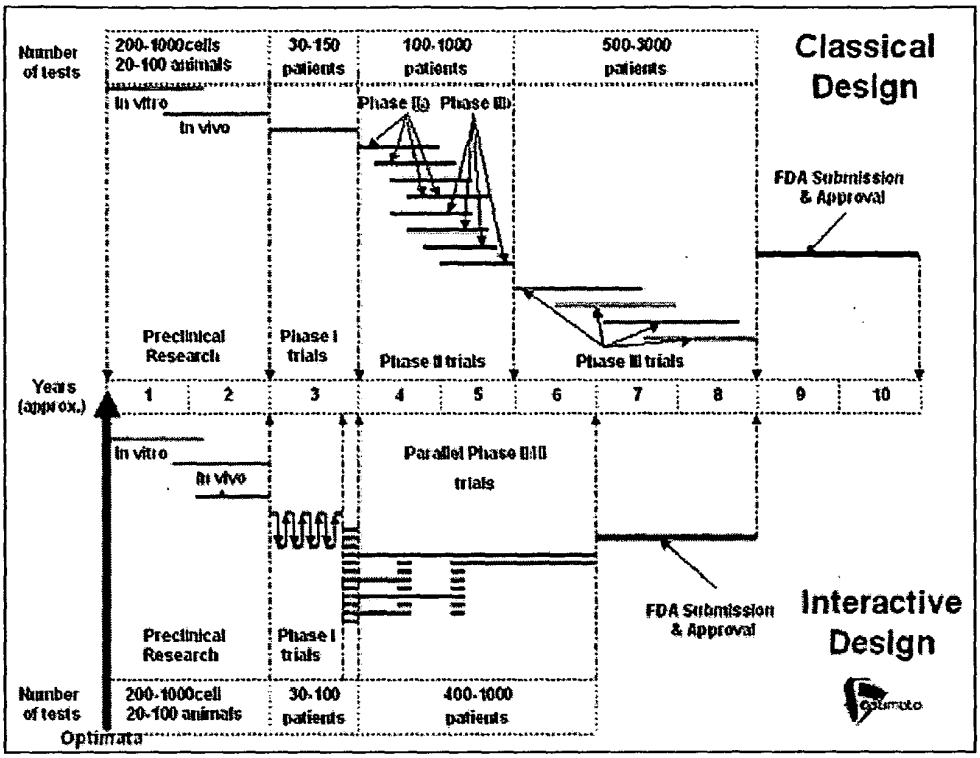
Number of tests
200-1000cells 20-100 animals
30-150 patients
100-1000 patients
500-3000 patients
Classical Design
In vitro
In vivo
Phase IIa
Phase IIb
FDA Submission & Approval
Preclinical Research
Phase I trials
Phase II trials
Phase III trials
Years (approx.)
1
2
3
4
5
6
7
8
9
10
In vitro
In vivo
Parallel Phase II/III trials
FDA Submission & Approval
Interactive Design
Preclinical Research
Phase I trials
Number of tests
200-1000cell 20-100 animals
30-100 patients
400-1000 patients
Optimata

Fig. 1.

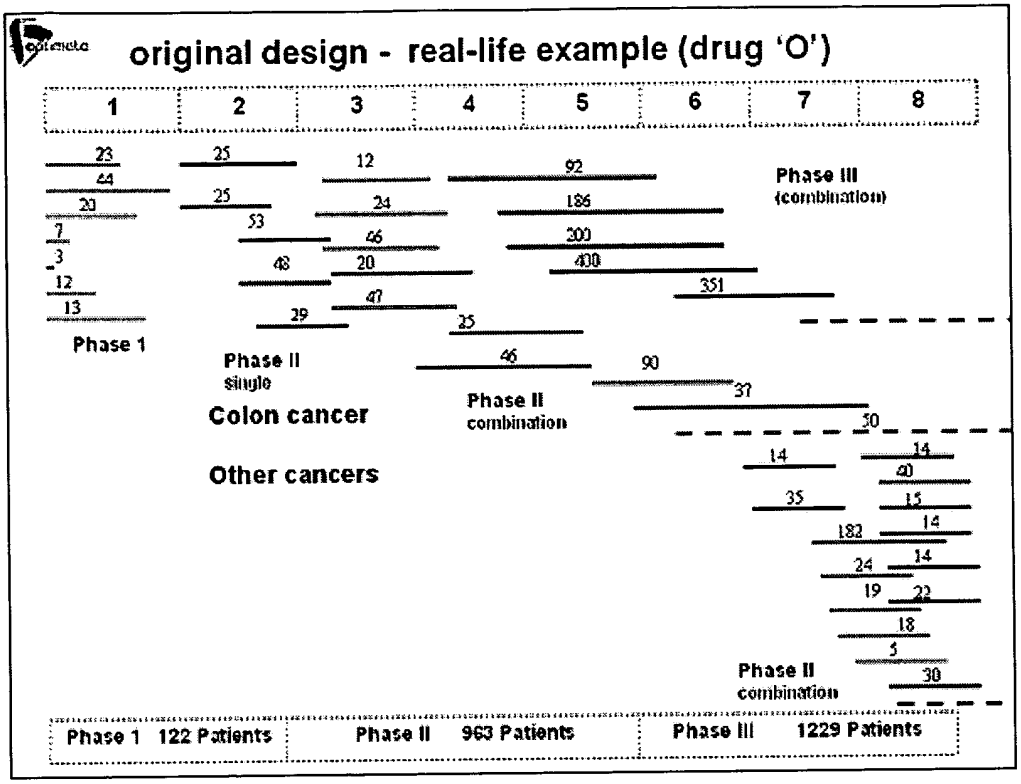
original design - real-life example (drug 'O')
1
2
3
4
5
6
7
8
23
44
20
7
3
12
13
25
25
53
48
29
12
24
46
20
47
25
92
186
300
400
351
46
90
37
Phase III
(combination)
Phase 1
Phase II
single
Colon cancer
Other cancers
Phase II
combination
30
14
35
182
24
19
18
5
14
40
15
14
14
22
Phase II
combination
30
Phase 1 122 Patients
Phase II 963 Patients
Phase III 1229 Patients

Fig.2A.

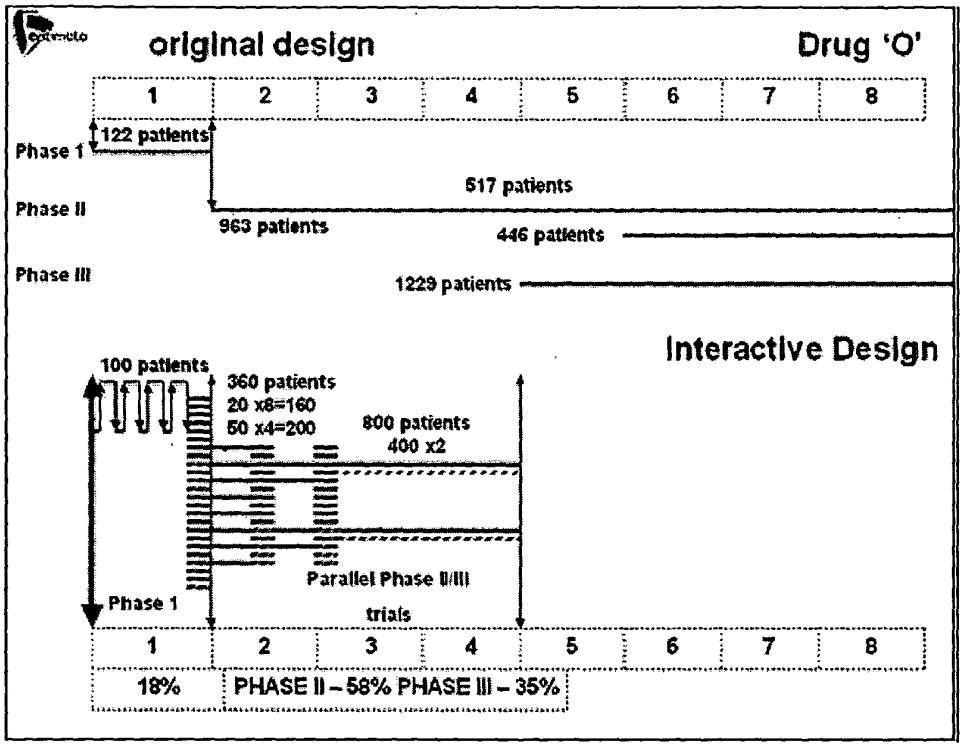
original design
Drug 'O'
1
2
3
4
5
6
7
8
Phase I
122 patients
Phase II
517 patients
963 patients
446 patients
Phase III
1229 patients
Interactive Design
100 patients
360 patients
20 x8=160
50 x4=200
800 patients
400 x2
Parallel Phase II/III
trials
Phase 1
1
2
3
4
5
6
7
8
18%
PHASE II – 58% PHASE III – 35%

Fig. 2B.

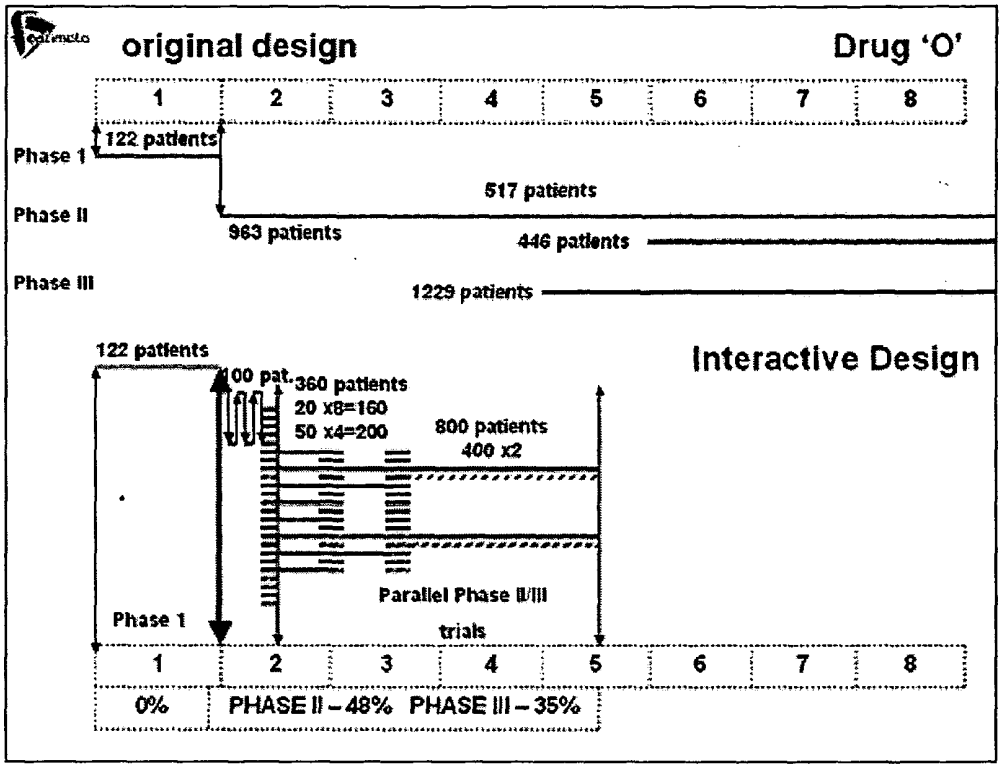
original design
Drug 'O'
1
2
3
4
5
6
7
8
Phase I
122 patients
517 patients
Phase II
963 patients
446 patients
Phase III
1229 patients
122 patients
Interactive Design
00 pat.
360 patients
20 x8=160
50 x4=200
800 patients
400 x2
Parallel Phase II/III
trials
Phase I
1
2
3
4
5
6
7
8
0%
PHASE II – 48%
PHASE III – 35%

Fig. 2C.

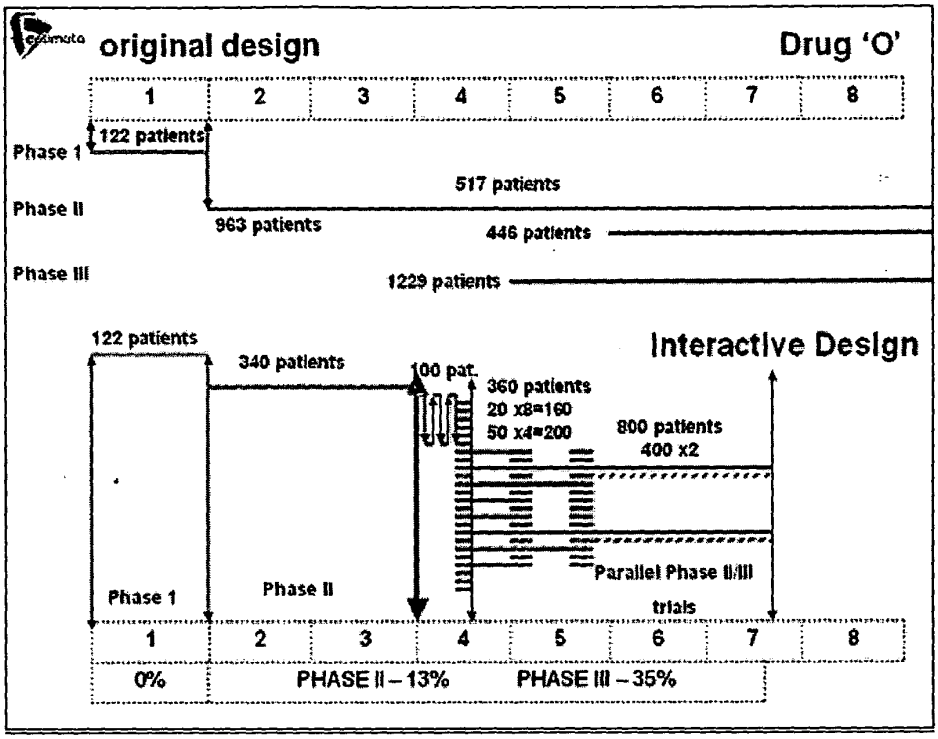
original design
Drug 'O'
1
2
3
4
5
6
7
8
122 patients
Phase I
517 patients
Phase II
963 patients
446 patients
Phase III
1229 patients
122 patients
Interactive Design
340 patients
100 pat.
360 patients
20 x8=160
50 x4=200
800 patients
400 x2
Parallel Phase II/III
trials
Phase I
Phase II
1
2
3
4
5
6
7
8
0%
PHASE II – 13%
PHASE III – 35%

Fig. 2D.

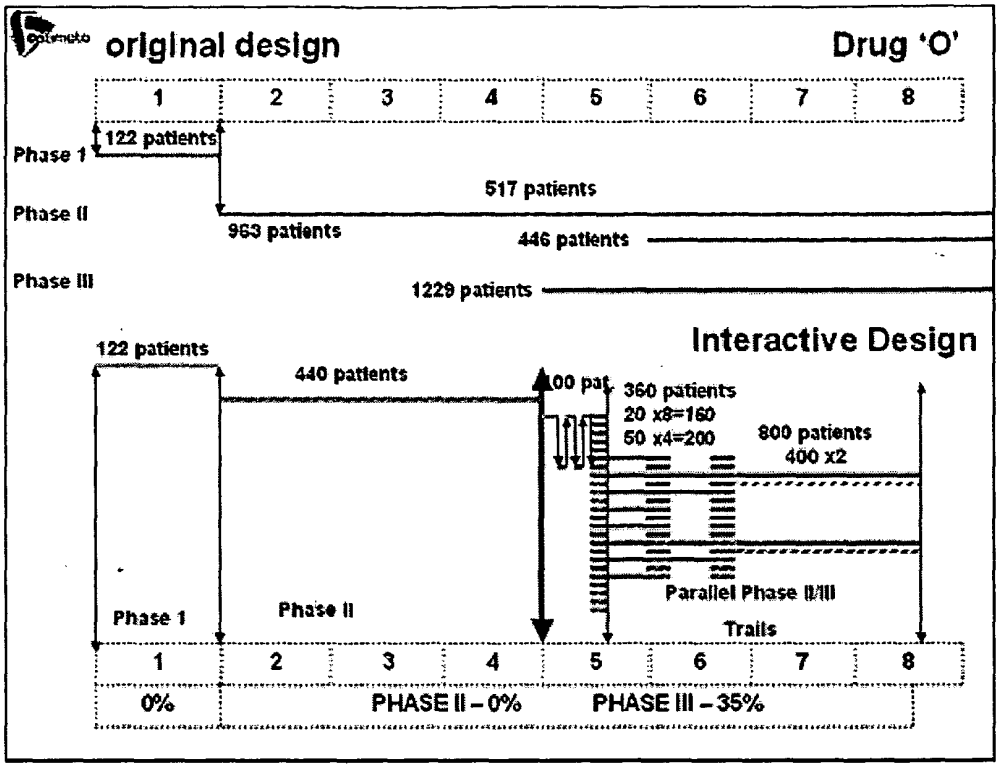
original design
Drug 'O'
1
2
3
4
5
6
7
8
122 patients
Phase I
517 patients
Phase II
953 patients
446 patients
Phase III
1229 patients
Interactive Design
122 patients
440 patients
360 patients
20 x8=160
50 x4=200
800 patients
400 x2
Parallel Phase II/III
Trails
Phase I
Phase II
0%
PHASE II – 0%
PHASE III – 35%

Fig. 2E.

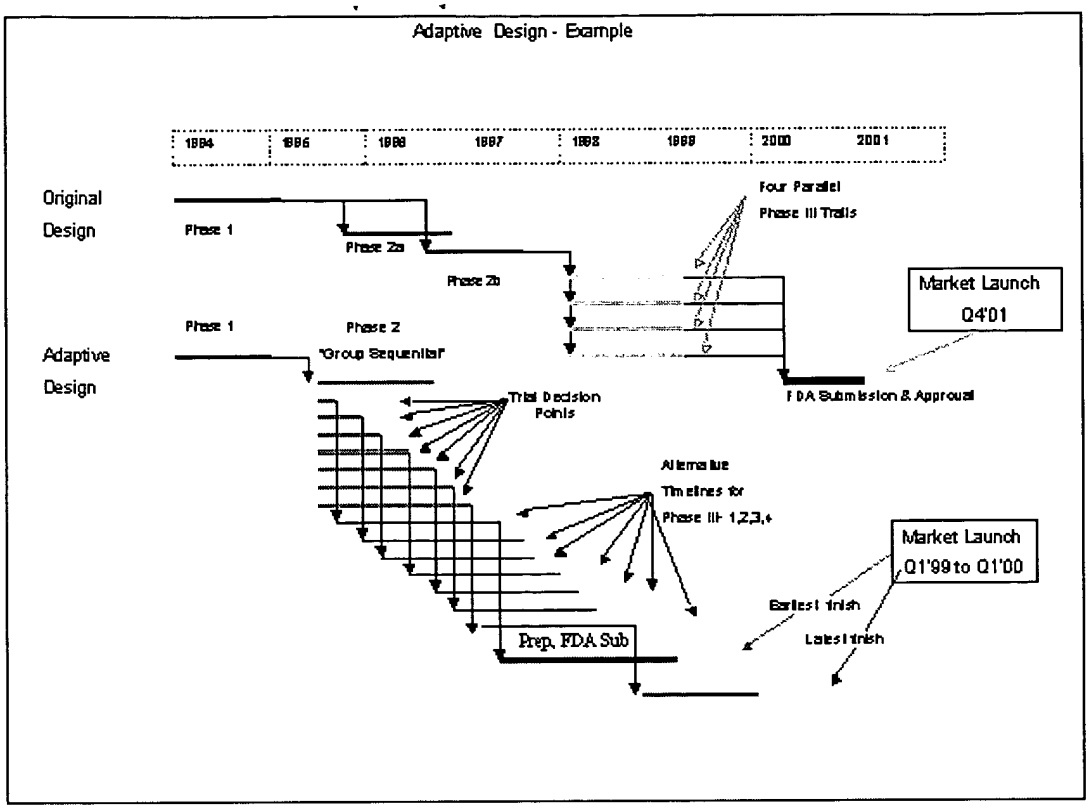
Adaptive Design - Example
1994
1996
1998
1997
1998
1999
2000
2001
Original
Design
Phase 1
Phase 2a
Phase 2b
Four Parallel
Phase III Trails
Market Launch
Q4'01
Phase 1
Phase 2
Adaptive
Design
"Group Sequential"
Trial Decision
Points
FDA Submission & Approval
Alternative
Timelines for
Phase III- 1,2,3,4
Market Launch
Q1'99 to Q1'00
Earliest finish
Latest finish
Prep. FDA Sub

Fig. 3.

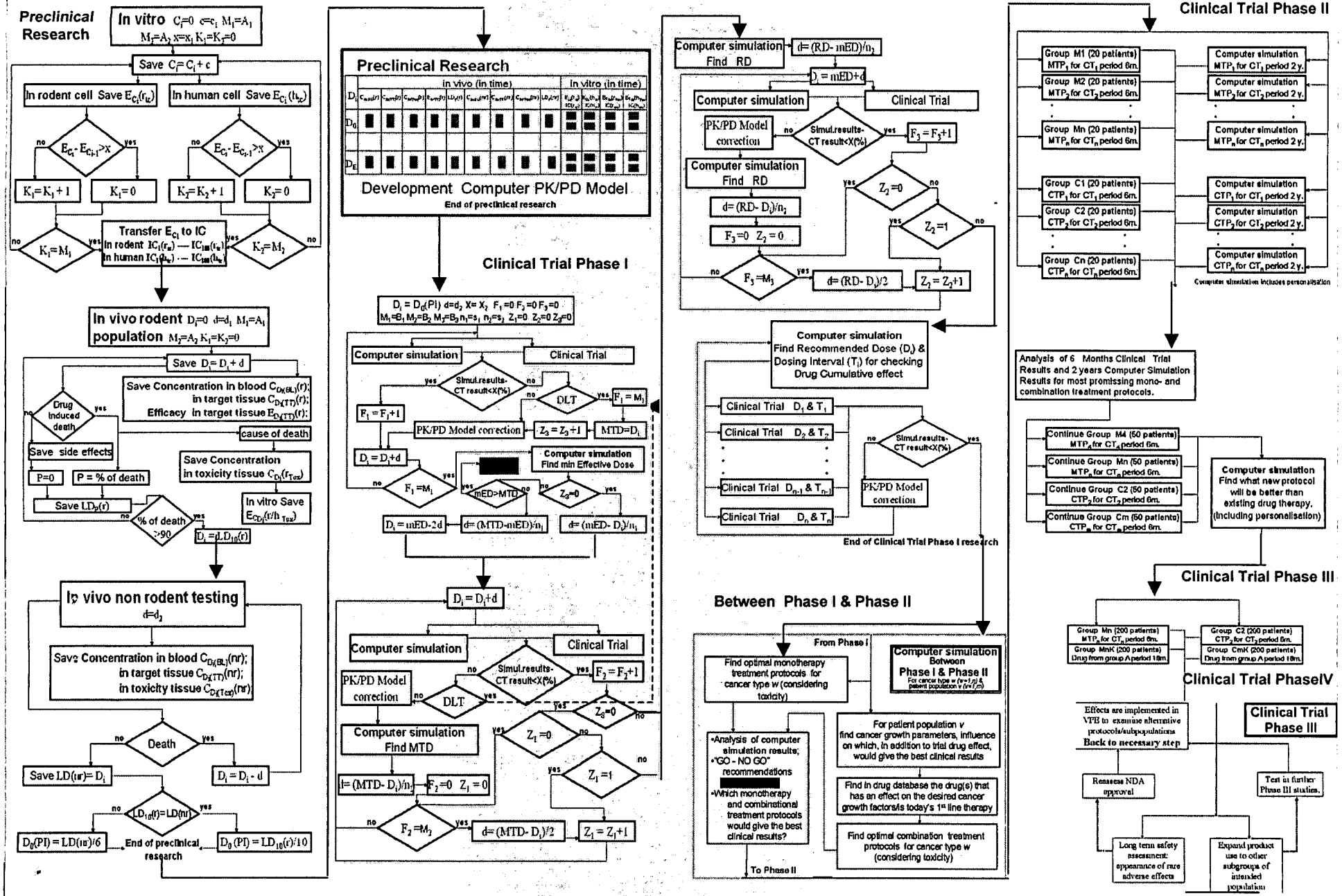
Preclinical Research
In vitro
Save
In rodent cell
In human cell
Transfer
In vivo rodent population
Drug induced death
Save side effects
Save Concentration in toxicity tissue
Save LD
% of death
In vivo non rodent testing
Death
Save LD(nr)
End of preclinical research
Preclinical Research
in vivo (in time)
in vitro (in time)
Development Computer PK/PD Model
End of preclinical research
Clinical Trial Phase I
Computer simulation
Clinical Trial
Simul.results-CT result<X(%)
DLT
PK/PD Model correction
Computer simulation Find min Effective Dose
Computer simulation Find MTD
Computer simulation Find RD
d= (RD- mED)/n
Computer simulation Find Recommended Dose (D) & Dosing Interval (T) for checking Drug Cumulative effect
Clinical Trial D & T
End of Clinical Trial Phase I research
Between Phase I & Phase II
From Phase I
Find optimal monotherapy treatment protocols for cancer type w (considering toxicity)
Computer simulation Between Phase I & Phase II
For patient population v find cancer growth parameters, influence on which, in addition to trial drug effect, would give the best clinical results
Find in drug database the drug(s) that has an effect on the desired cancer growth factors/is today's 1st line therapy
Find optimal combination treatment protocols for cancer type w (considering toxicity)
•Analysis of computer simulation results;
•"GO - NO GO" recommendations
•Which monotherapy and combinational treatment protocols would give the best clinical results?
To Phase II
Clinical Trial Phase II
Group M1 (20 patients) MTP1 for CT1 period 6m.
Group M2 (20 patients) MTP2 for CT2 period 6m.
Group Mn (20 patients) MTPn for CTn period 6m.
Group C1 (20 patients) CTP1 for CT1 period 6m.
Group C2 (20 patients) CTP2 for CT2 period 6m.
Group Cn (20 patients) CTPn for CTn period 6m.
Computer simulation MTP1 for CT1 period 2 y.
Computer simulation MTP2 for CT2 period 2 y.
Computer simulation MTPn for CTn period 2 y.
Computer simulation CTP1 for CT1 period 2 y.
Computer simulation CTP2 for CT2 period 2 y.
Computer simulation CTPn for CTn period 2 y.
Computer simulation includes personalisation
Analysis of 6 Months Clinical Trial Results and 2 years Computer Simulation Results for most promissing mono- and combination treatment protocols.
Continue Group M4 (50 patients) MTP4 for CT4 period 6m.
Continue Group Mn (50 patients) MTPn for CTn period 6m.
Continue Group C2 (50 patients) CTP2 for CT2 period 6m.
Continue Group Cm (50 patients) CTPm for CTm period 6m.
Computer simulation Find what new protocol will be better than existing drug therapy. (including personalisation)
Clinical Trial Phase III
Group Mn (200 patients) MTPn for CTn period 6m.
Group MnK (200 patients) Drug from group A period 18m.
Group C2 (200 patients) CTP2 for CT2 period 6m.
Group CmK (200 patients) Drug from group A period 18m.
Clinical Trial PhaseIV
Effects are implemented in VPH to examine alternative protocols/subpopulations
Back to necessary step
Clinical Trial Phase III
Reassess NDA approval
Test in further Phase III studies.
Long term safety assessment: appearance of rare adverse effects
Expand product use to other subgroups of intended population

Fig. 4

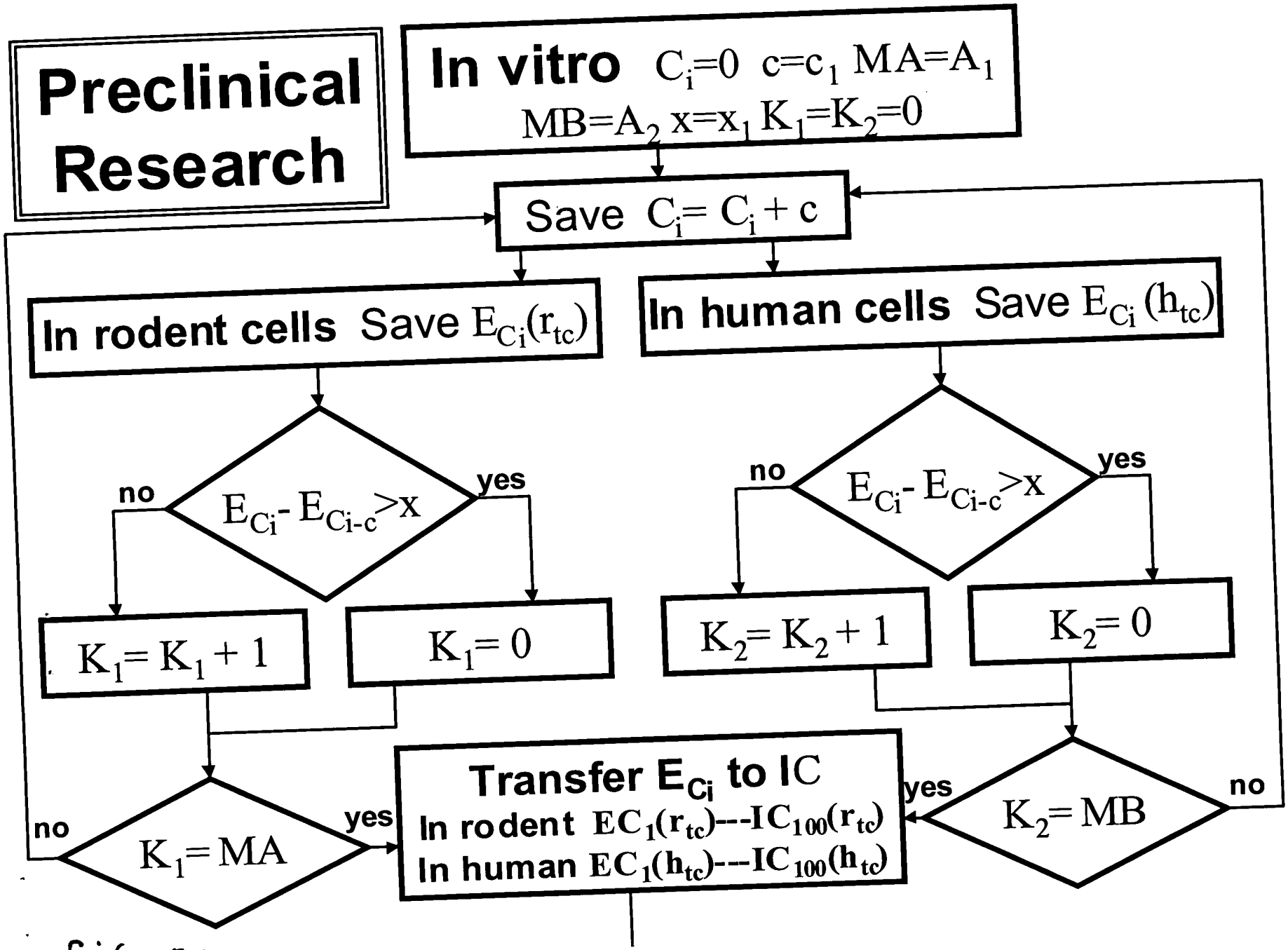
Preclinical Research
In vitro $C_i=0$ $c=c_1$ $MA=A_1$ $MB=A_2$ $x=x_1$ $K_1=K_2=0$
Save $C_i = C_i + c$
In rodent cells Save $E_{Ci}(r_{tc})$
In human cells Save $E_{Ci}(h_{tc})$
$E_{Ci} - E_{Ci-c} > x$
no
yes
$K_1 = K_1 + 1$
$K_1 = 0$
$E_{Ci} - E_{Ci-c} > x$
no
yes
$K_2 = K_2 + 1$
$K_2 = 0$
$K_1 = MA$
no
yes
Transfer E_{Ci} to IC
In rodent $EC_1(r_{tc})$---$IC_{100}(r_{tc})$
In human $EC_1(h_{tc})$---$IC_{100}(h_{tc})$
$K_2 = MB$
yes
no

fig. 5A

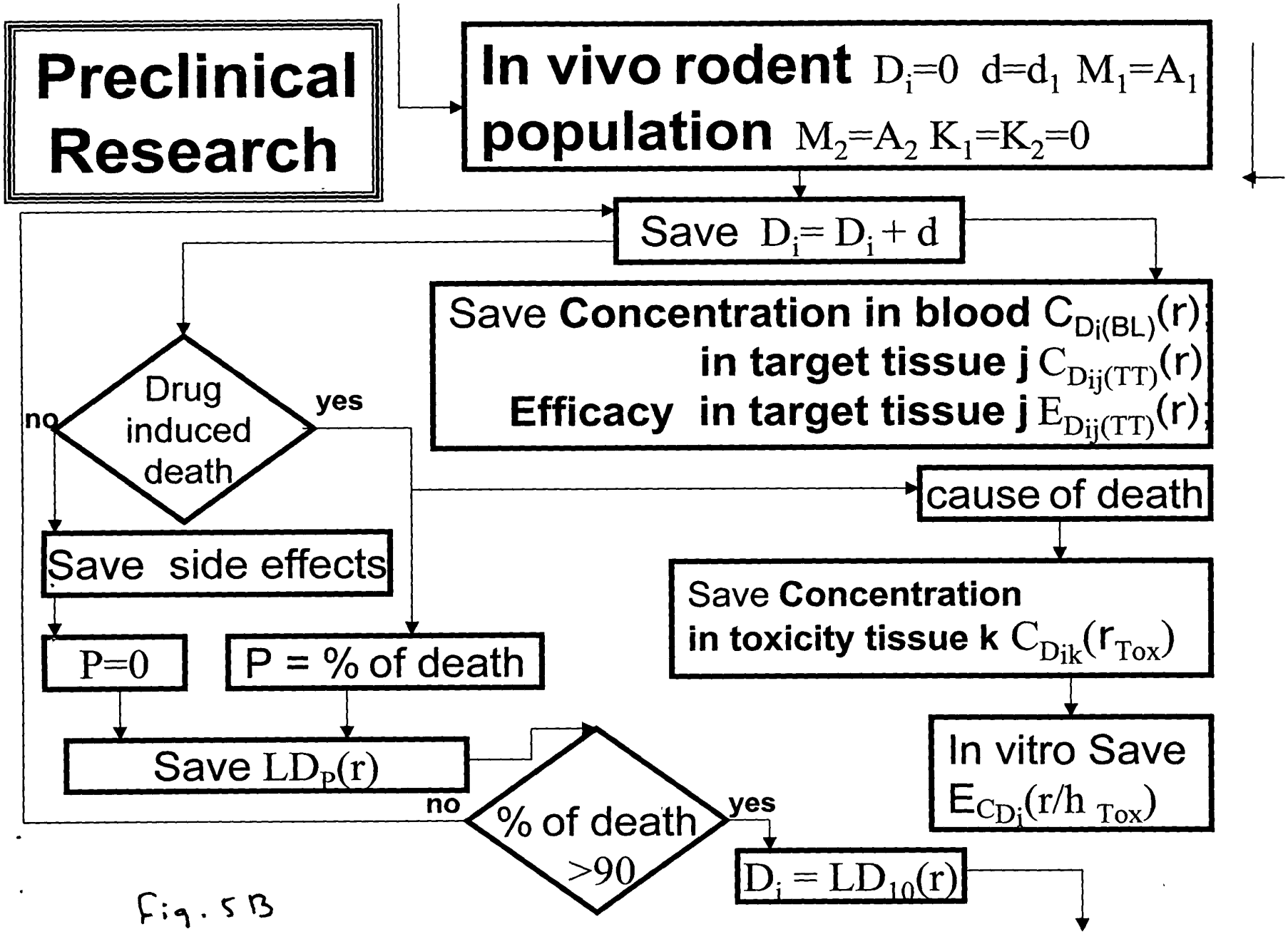
Preclinical Research
In vivo rodent $D_i=0$ $d=d_1$ $M_1=A_1$
population $M_2=A_2$ $K_1=K_2=0$
Save $D_i = D_i + d$
Save Concentration in blood $C_{Di(BL)}(r)$
in target tissue j $C_{Dij(TT)}(r)$
Efficacy in target tissue j $E_{Dij(TT)}(r)$
Drug induced death
no
yes
cause of death
Save side effects
Save Concentration
in toxicity tissue k $C_{Dik}(r_{Tox})$
P=0
P = % of death
In vitro Save
$E_{CDi}(r/h_{Tox})$
Save $LD_P(r)$
% of death >90
no
yes
$D_i = LD_{10}(r)$

Fig. 5B

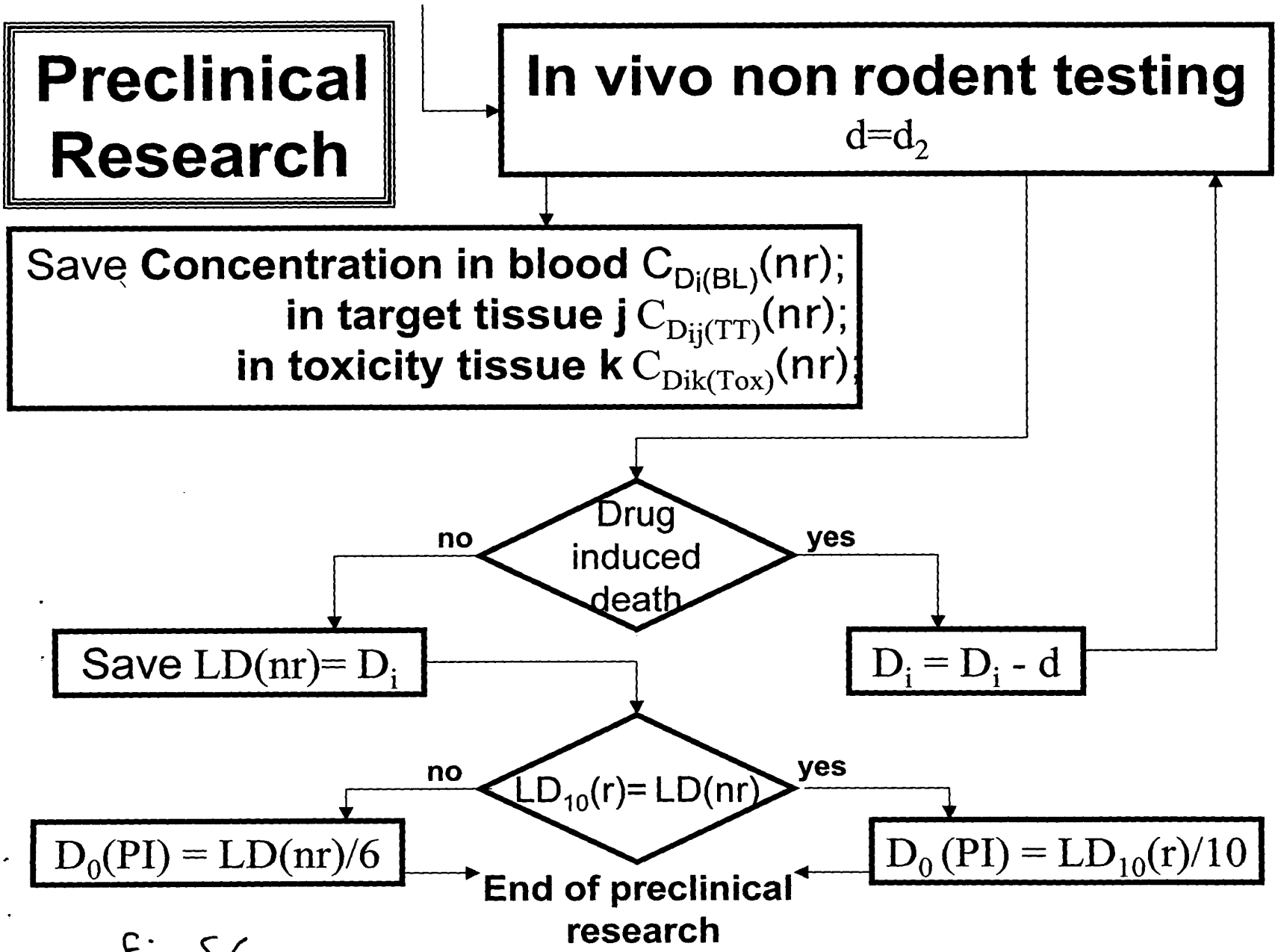
Preclinical Research
In vivo non rodent testing
d=d2
Save Concentration in blood CDi(BL)(nr);
in target tissue j CDij(TT)(nr);
in toxicity tissue k CDik(Tox)(nr);
Drug induced death
no
yes
Save LD(nr)= Di
Di = Di - d
LD10(r)= LD(nr)
no
yes
D0(PI) = LD(nr)/6
D0 (PI) = LD10(r)/10
End of preclinical research

Fig. 5C

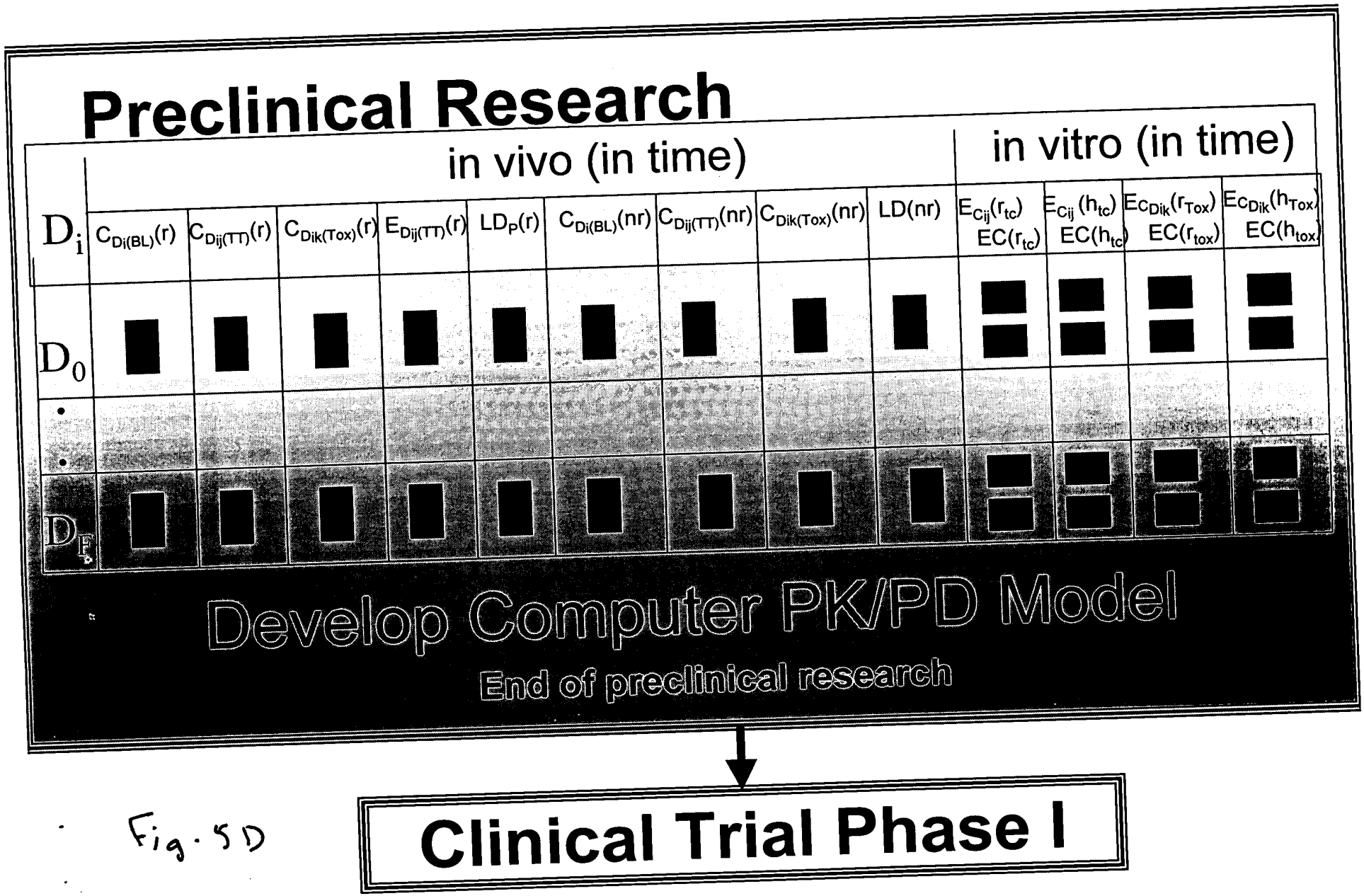
Preclinical Research
in vivo (in time)
in vitro (in time)
D_i
$C_{Di(BL)}(r)$
$C_{Dij(TT)}(r)$
$C_{Dik(Tox)}(r)$
$E_{Dij(TT)}(r)$
$LD_P(r)$
$C_{Di(BL)}(nr)$
$C_{Dij(TT)}(nr)$
$C_{Dik(Tox)}(nr)$
LD(nr)
$E_{Cij}(r_{tc})$ $EC(r_{tc})$
$E_{Cij}(h_{tc})$ $EC(h_{tc})$
$E_{CDik}(r_{Tox})$ $EC(r_{tox})$
$E_{CDik}(h_{Tox})$ $EC(h_{tox})$
D_0
D_F
Develop Computer PK/PD Model
End of preclinical research
Clinical Trial Phase I

Fig. 5D

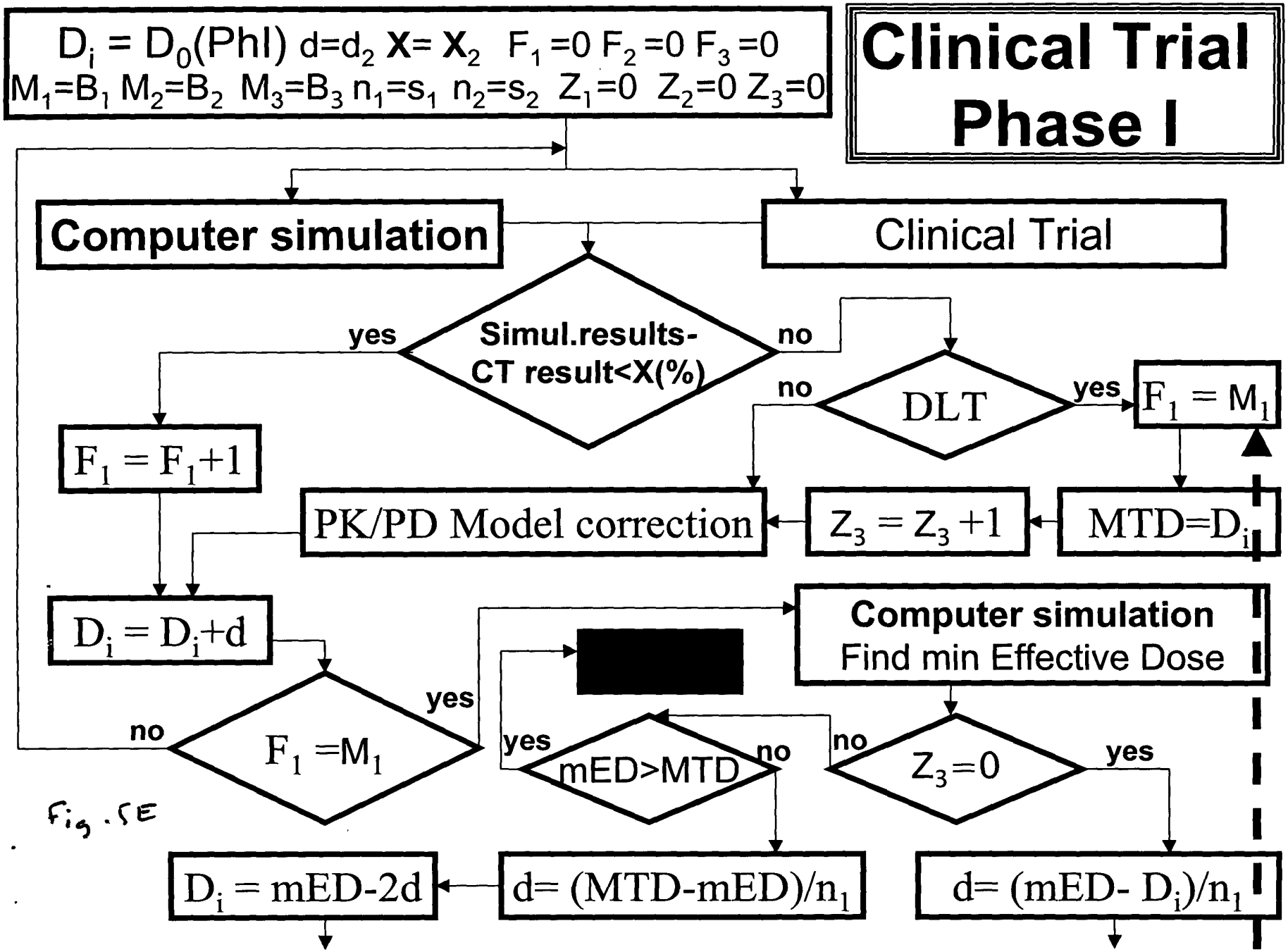
$D_i = D_0$(PhI) d=d_2 X= X_2 F_1=0 F_2=0 F_3=0
$M_1=B_1$ $M_2=B_2$ $M_3=B_3$ $n_1=s_1$ $n_2=s_2$ Z_1=0 Z_2=0 Z_3=0
Clinical Trial Phase I
Computer simulation
Clinical Trial
Simul.results-CT result<X(%)
yes
no
DLT
yes
no
$F_1 = M_1$
$F_1 = F_1+1$
PK/PD Model correction
$Z_3 = Z_3 +1$
MTD=D_i
$D_i = D_i+d$
Computer simulation
Find min Effective Dose
yes
no
$F_1 = M_1$
yes
mED>MTD
no
no
Z_3=0
yes
D_i = mED-2d
d= (MTD-mED)/n_1
d= (mED- D_i)/n_1

Fig. 5E

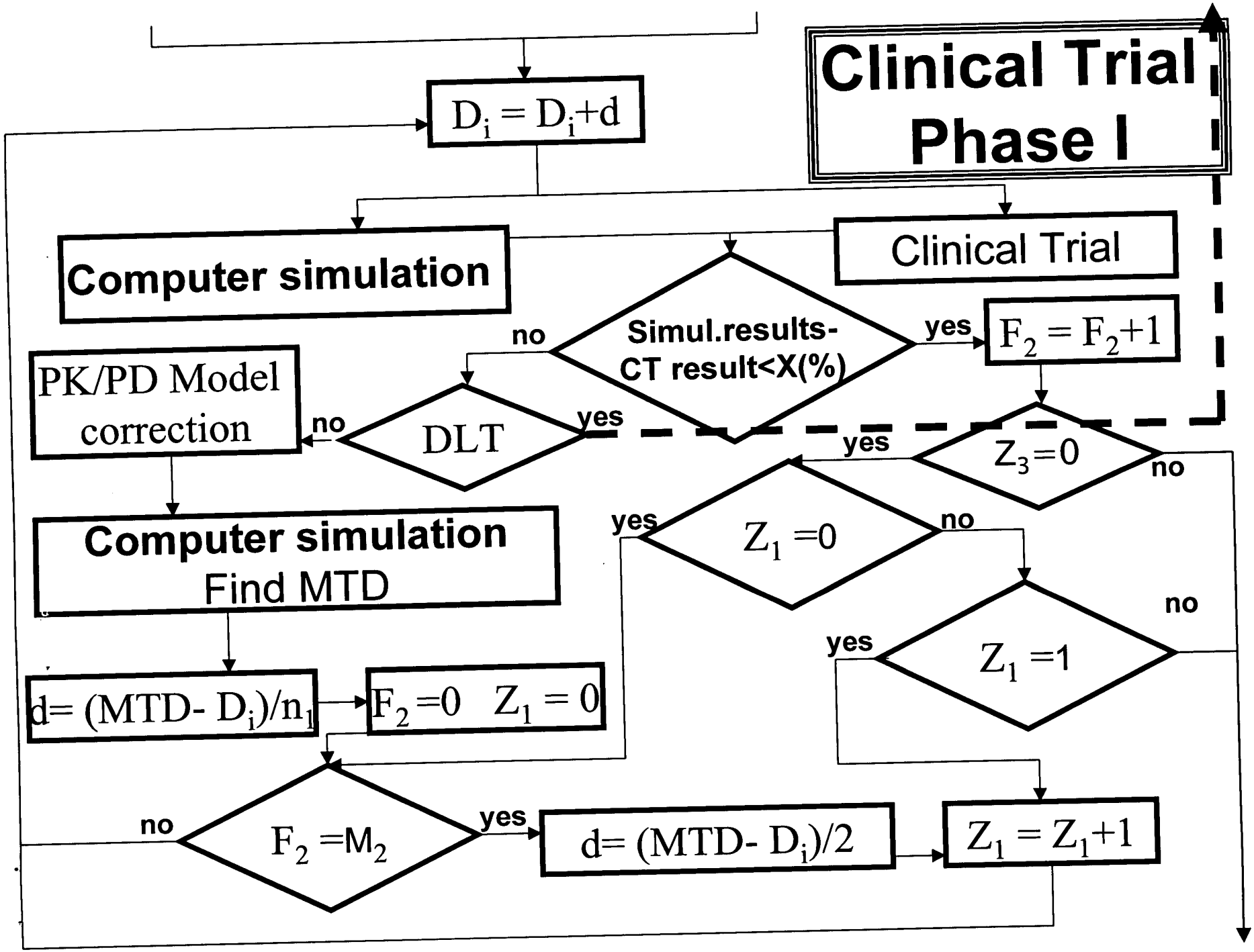
Clinical Trial Phase I
$D_i = D_i + d$
Computer simulation
Clinical Trial
Simul.results- CT result<X(%)
no
yes
$F_2 = F_2 + 1$
PK/PD Model correction
no
DLT
yes
yes
$Z_3 = 0$
no
Computer simulation Find MTD
yes
$Z_1 = 0$
no
no
yes
$Z_1 = 1$
$d = (MTD - D_i)/n_1$
$F_2 = 0 \quad Z_1 = 0$
no
$F_2 = M_2$
yes
$d = (MTD - D_i)/2$
$Z_1 = Z_1 + 1$

Fig. 5F

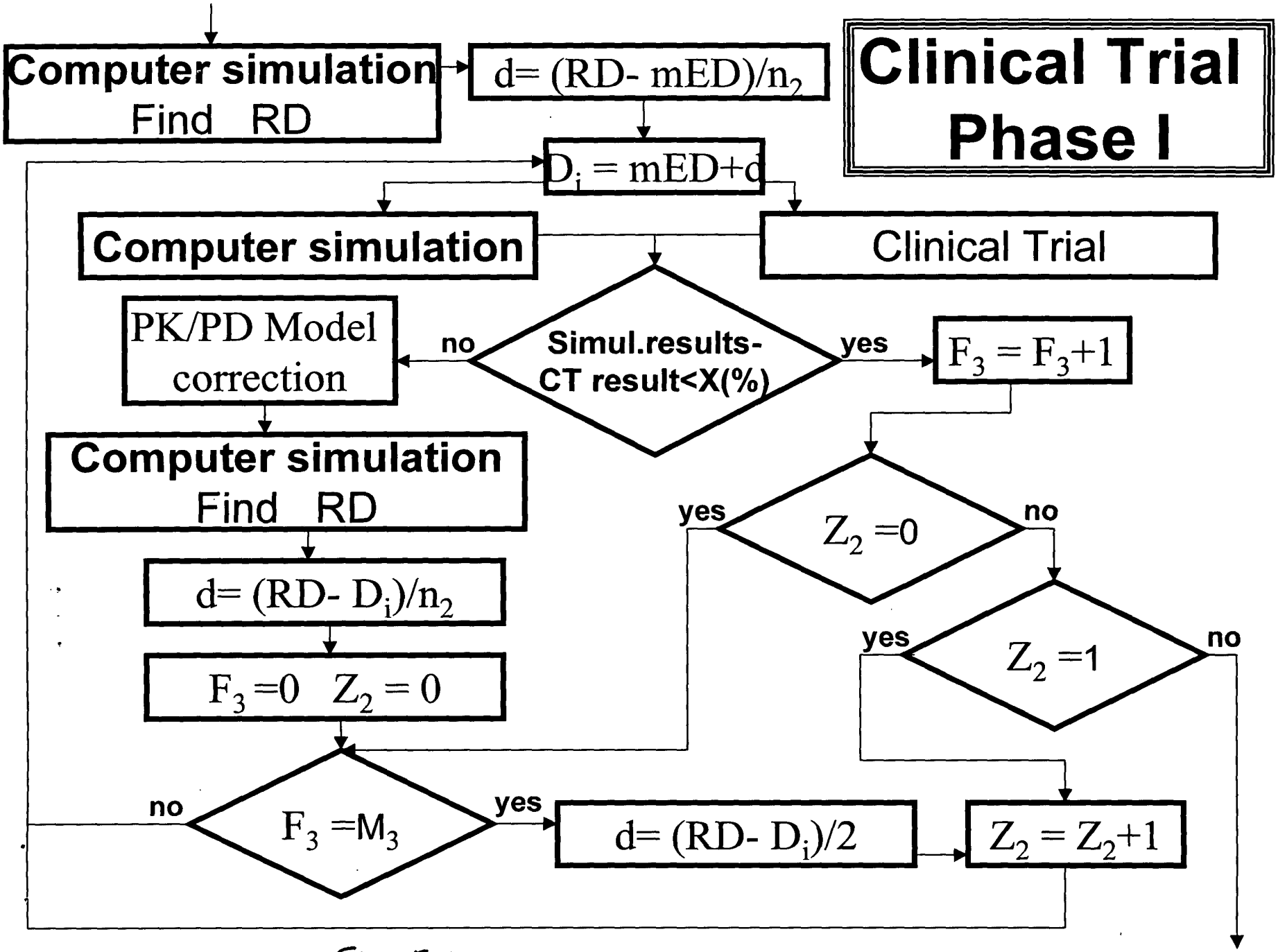
Computer simulation
Find RD
d= (RD- mED)/n2
Clinical Trial
Phase I
Di = mED+d
Computer simulation
Clinical Trial
PK/PD Model
correction
no
Simul.results-
CT result<X(%)
yes
F3 = F3+1
Computer simulation
Find RD
yes
Z2 =0
no
d= (RD- Di)/n2
yes
Z2 =1
no
F3 =0 Z2 = 0
no
F3 =M3
yes
d= (RD- Di)/2
Z2 = Z2+1

Fig 5a

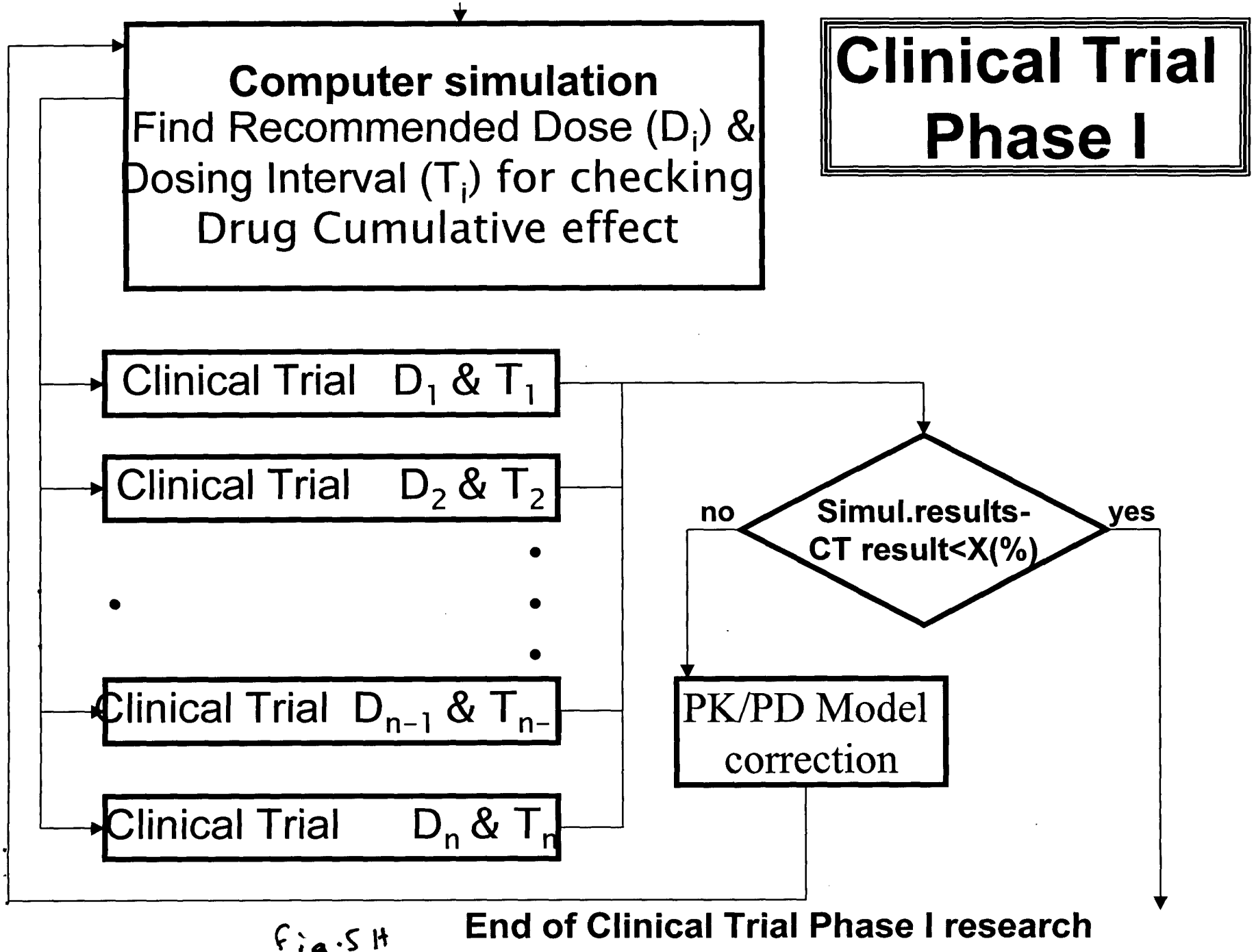
Clinical Trial Phase I
Computer simulation
Find Recommended Dose (D_i) &
Dosing Interval (T_i) for checking
Drug Cumulative effect
Clinical Trial D_1 & T_1
Clinical Trial D_2 & T_2
Clinical Trial D_{n-1} & T_{n-}
Clinical Trial D_n & T_n
Simul.results-
CT result<X(%)
no
yes
PK/PD Model
correction
End of Clinical Trial Phase I research

Fig.5 H

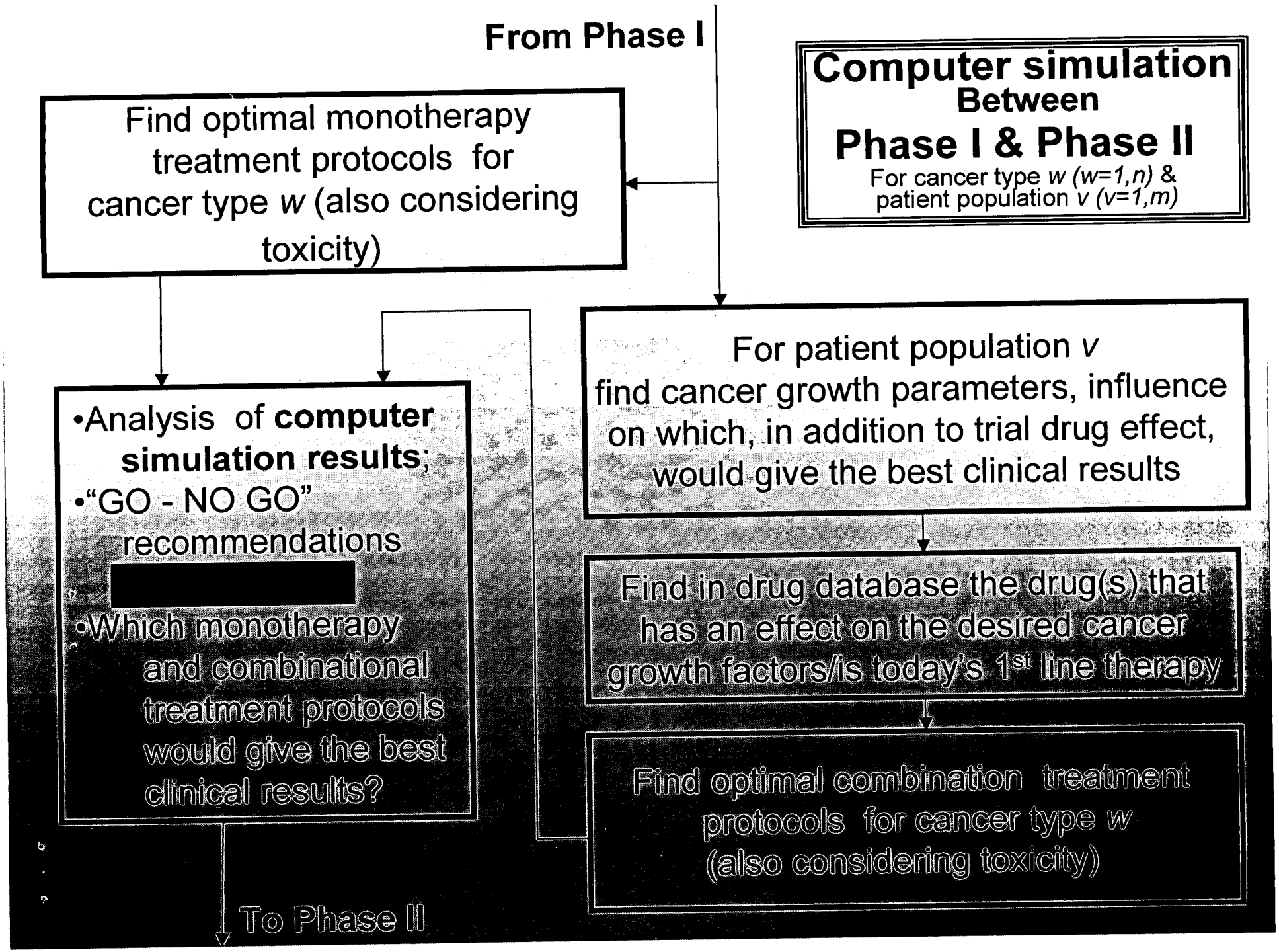
From Phase I
Computer simulation
Between
Phase I & Phase II
For cancer type w (w=1,n) &
patient population v (v=1,m)
Find optimal monotherapy
treatment protocols for
cancer type w (also considering
toxicity)
For patient population v
find cancer growth parameters, influence
on which, in addition to trial drug effect,
would give the best clinical results
•Analysis of computer
simulation results;
•"GO - NO GO"
recommendations
•Which monotherapy
and combinational
treatment protocols
would give the best
clinical results?
Find in drug database the drug(s) that
has an effect on the desired cancer
growth factors/is today's 1st line therapy
Find optimal combination treatment
protocols for cancer type w
(also considering toxicity)
To Phase II

Fig. 5I

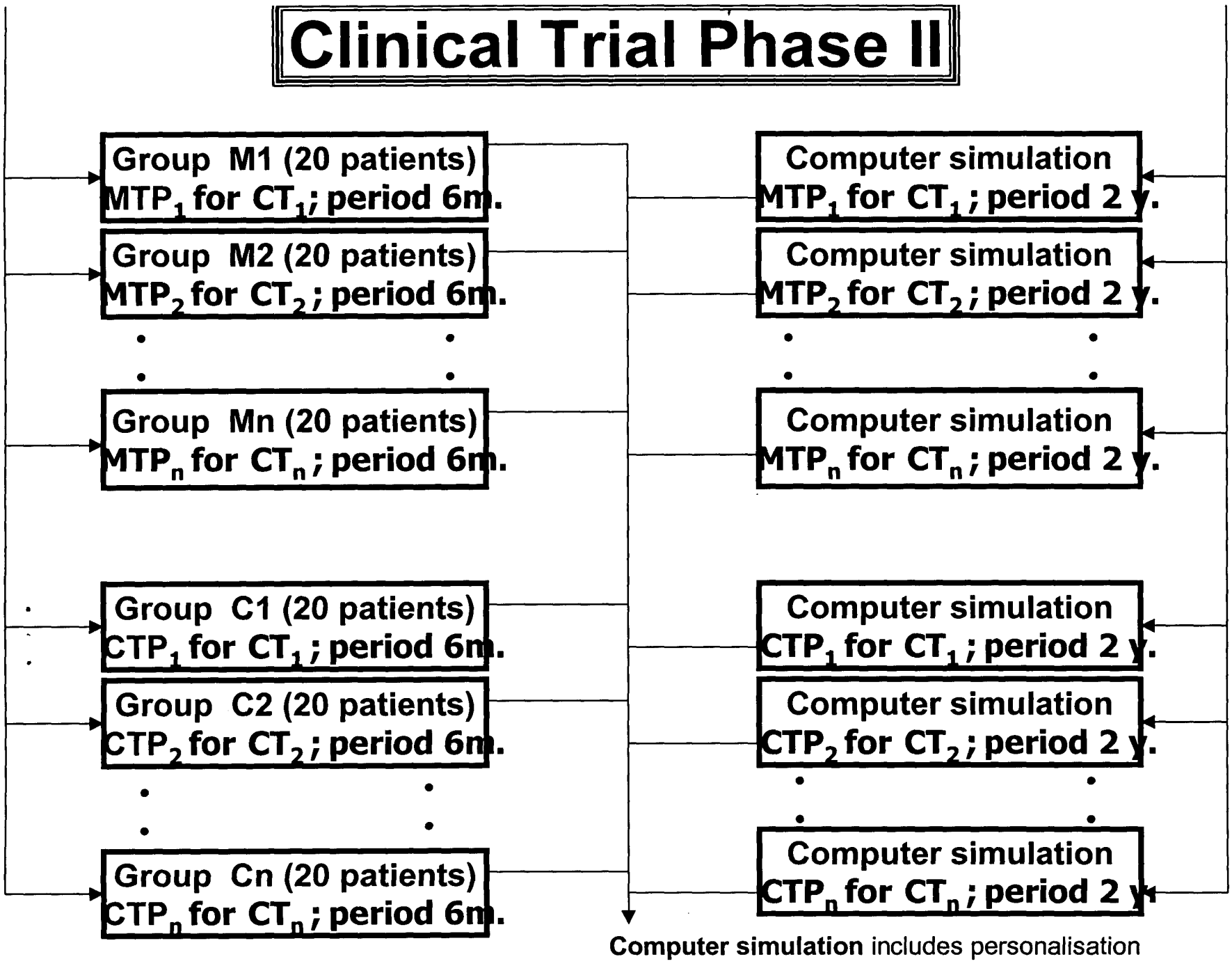
Clinical Trial Phase II
Group M1 (20 patients) MTP1 for CT1; period 6m.
Group M2 (20 patients) MTP2 for CT2; period 6m.
Group Mn (20 patients) MTPn for CTn; period 6m.
Group C1 (20 patients) CTP1 for CT1; period 6m.
Group C2 (20 patients) CTP2 for CT2; period 6m.
Group Cn (20 patients) CTPn for CTn; period 6m.
Computer simulation MTP1 for CT1; period 2 y.
Computer simulation MTP2 for CT2; period 2 y.
Computer simulation MTPn for CTn; period 2 y.
Computer simulation CTP1 for CT1; period 2 y.
Computer simulation CTP2 for CT2; period 2 y.
Computer simulation CTPn for CTn; period 2 y.
Computer simulation includes personalisation

Fig. 55

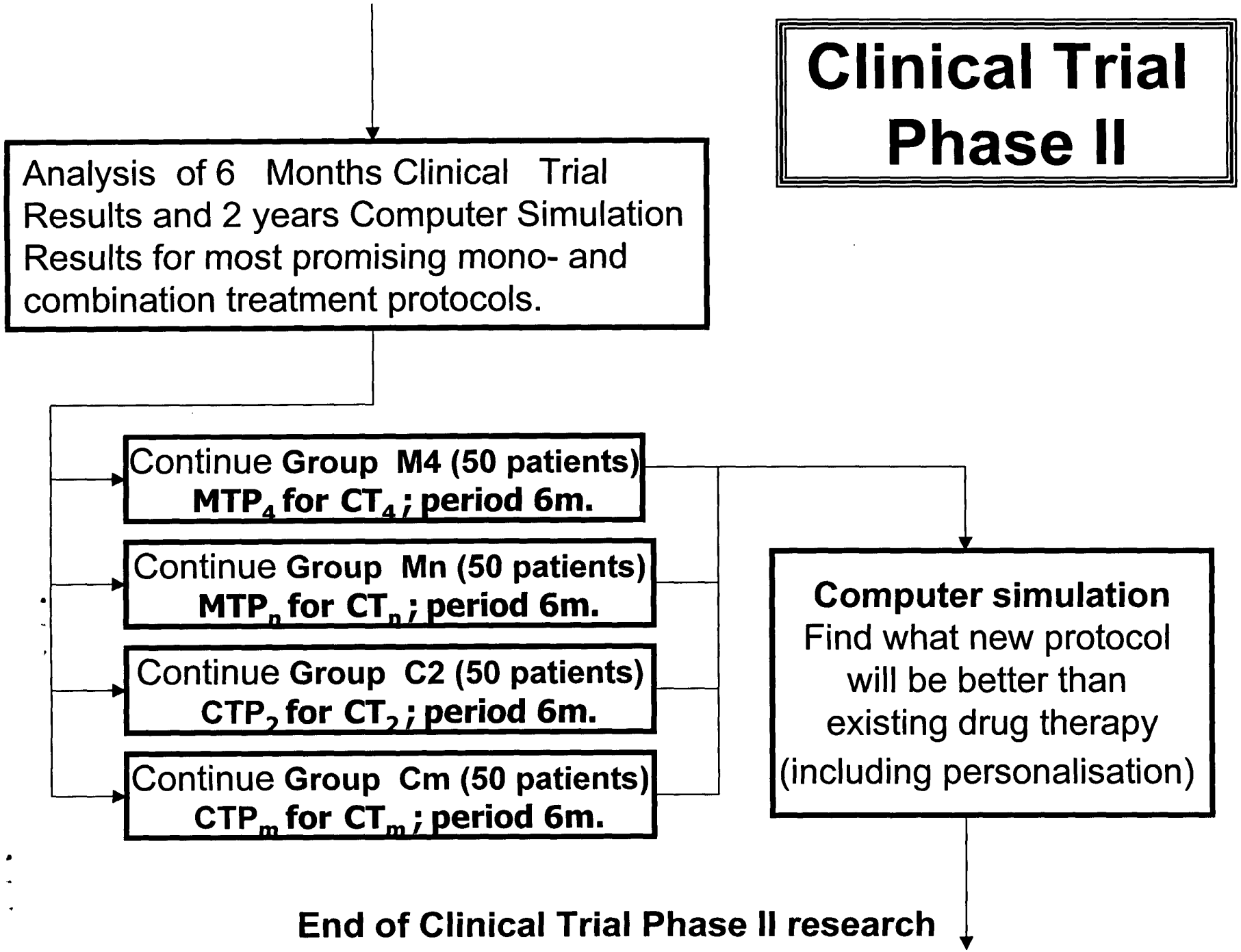
Clinical Trial Phase II
Analysis of 6 Months Clinical Trial Results and 2 years Computer Simulation Results for most promising mono- and combination treatment protocols.
Continue Group M4 (50 patients) MTP4 for CT4; period 6m.
Continue Group Mn (50 patients) MTPn for CTn; period 6m.
Continue Group C2 (50 patients) CTP2 for CT2; period 6m.
Continue Group Cm (50 patients) CTPm for CTm; period 6m.
Computer simulation Find what new protocol will be better than existing drug therapy (including personalisation)
End of Clinical Trial Phase II research

Fig. 5k

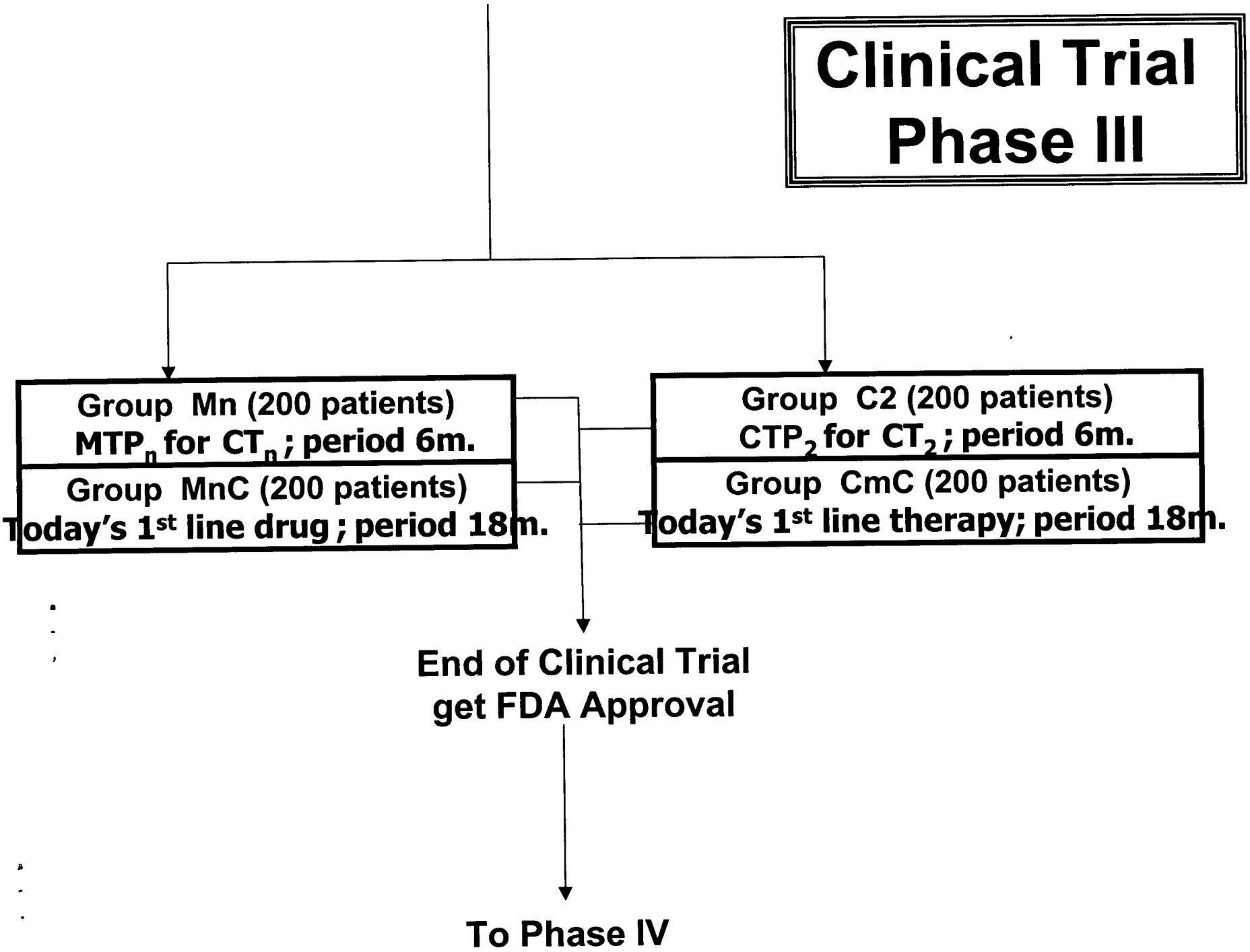
Clinical Trial
Phase III
Group Mn (200 patients)
MTP$_n$ for CT$_n$; period 6m.
Group MnC (200 patients)
Today's 1st line drug ; period 18m.
Group C2 (200 patients)
CTP$_2$ for CT$_2$; period 6m.
Group CmC (200 patients)
Today's 1st line therapy; period 18m.
End of Clinical Trial
get FDA Approval
To Phase IV

Fig. 5L

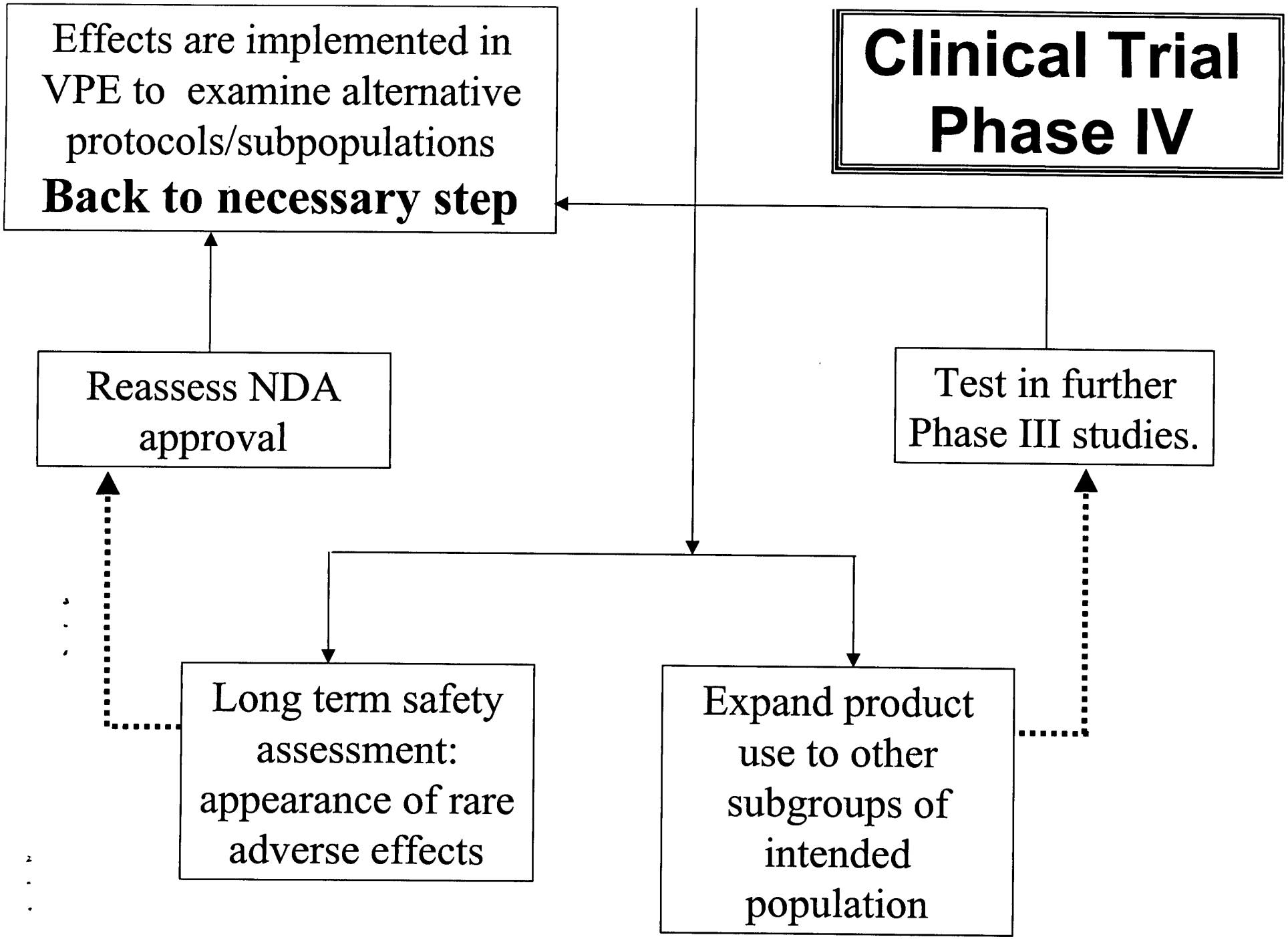
Clinical Trial
Phase IV
Effects are implemented in VPE to examine alternative protocols/subpopulations
Back to necessary step
Reassess NDA approval
Test in further Phase III studies.
Long term safety assessment: appearance of rare adverse effects
Expand product use to other subgroups of intended population

Fig .5M

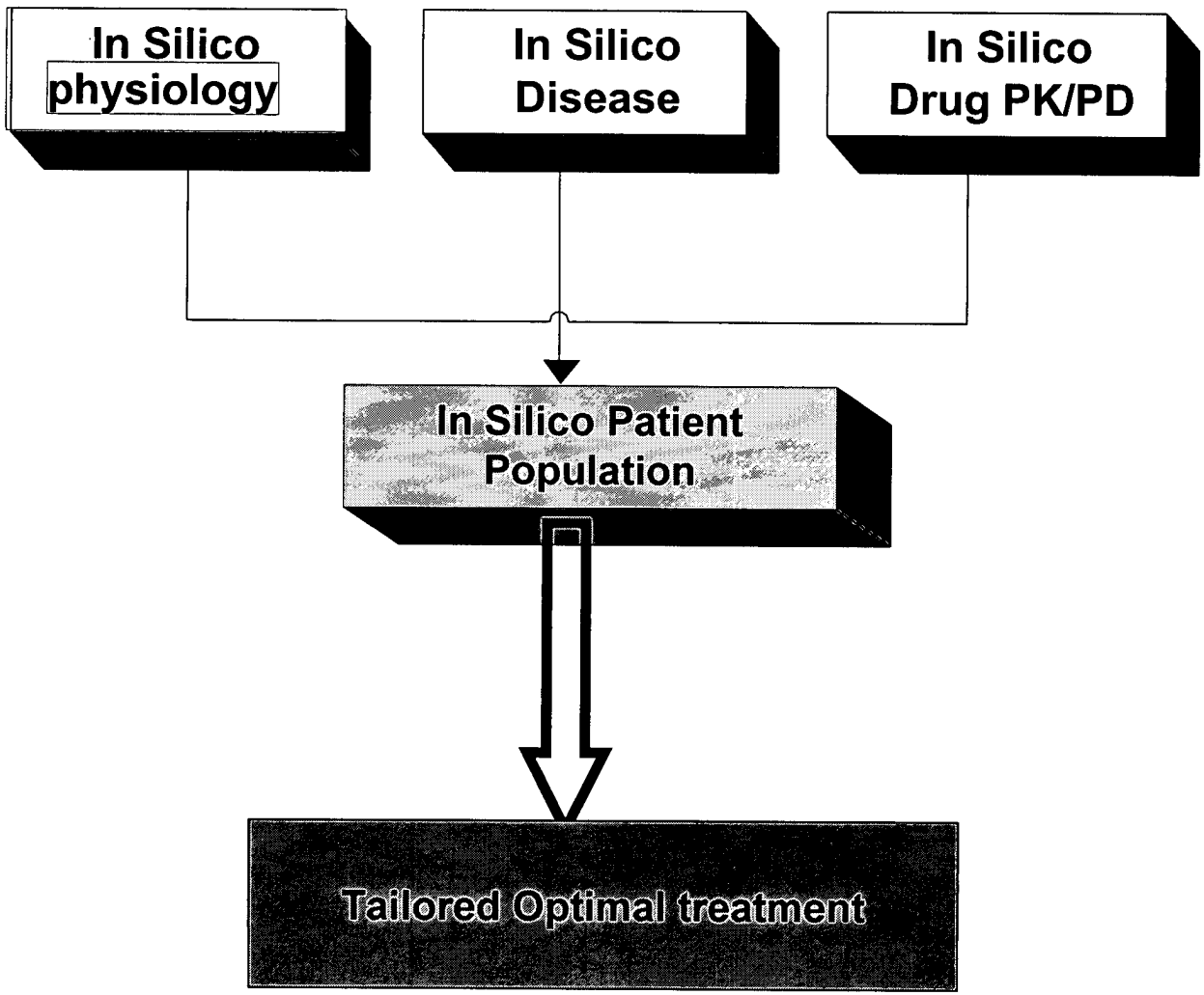
In Silico physiology
In Silico Disease
In Silico Drug PK/PD
In Silico Patient Population
Tailored Optimal treatment

Fig. 6